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Kessler H. Detection of hindered rotation and inversion by NMR spectroscopy. *Angew. Chem. Int. Ed.* 9:219-35, 1970.
[Chemisches Institut, Universität Tübingen, Federal Republic of Germany]

This article describes the use of NMR line shape analysis to study rates of intramolecular processes and its application to rotations and inversions in organic molecules. Substituent effects can be used to elucidate mechanistic details and for the prediction of the stability of conformations against mutual interconversions. [The *SCI*® indicates that this paper has been cited in more than 550 publications.]

Molecular Mobility by NMR

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As a young postdoc fellow at the University of Tübingen, Germany, I wanted to become independent and do something different from that of my supervisor, E. Müller. So I pursued the study of dynamic processes by NMR spectroscopy—a topic that was completely foreign to Müller.

I found a number of rotation and inversion processes that could not be studied by other techniques. Intensive collaboration with synthetic chemists in Tübingen, especially A. Rieker, and my own synthetic work led to a number of publications in the field, all written in German. I soon realized that this work was not well recognized in the scientific world and therefore decided to write a key paper in English. However, as I grew up in East Germany, learning only Russian and Latin in school, my English was even worse than it is now. As the *Angewandte Chemie* provided translation, I wrote the article, which of course cited not only our own work, but served as a review of work from many laboratories.

At that time, most organic chemists were not so aware of the merits of dynamic NMR and had no "feeling" about barrier heights. The paper filled a gap and found immediate recognition. Suddenly, I was considered an "expert in the field." The article certainly contributed to the fact that I got an offer for a chair in organic chemistry at the J.W. Goethe University in Frankfurt at the age of 30. I remained there for 18 years until I moved to the Technische Universität München.

The article describes the evaluation of exchange-broadened NMR spectra to obtain kinetic data and their use to elucidate conformational equilibria and mechanistic pathways. The advantage of the methodology is that it fills a gap because free energies of interconversions, which are too fast to separate, could not be determined by other techniques. This medium range (5 to 25 kcals) is especially interesting for chemists because a systematic study of substituent effects helps to understand preferred conformations, mechanistic details of interconversions, and stability of structures. For example, it was possible to provide evidence for the preferred mechanism of syn-anti-isomerism to be an inversion at the planar nitrogen (via a linear transition state) rather than a rotation about the CN double bond.[1] Substituent effects on rates are now well understood. That has allowed the prediction of rates in many compounds of interest.

It was mainly timing that led to the great reception of the article. Later on, several books appeared on this topic (see, for example, reference 1). Ten years later, my research interest switched to conformational studies of bioactive peptides,[2,3] using and developing multidimensional NMR techniques.[4] Reading the literature, I still follow the study of dynamic NMR (DNMR), but I am now more involved in two-dimensional NMR (2D-NMR) and recently even in 3D-NMR.[5]

1. **Öki M.** *Applications of dynamic NMR spectroscopy to organic chemistry.* New York: VCH, 1985. (Cited 80 times.)
2. **Loosli H R, Kessler H, Oschkinat H, Weber H P, Petcher T J & Widmer A.** Peptide conformations, 31. The conformation of cyclosporin A in the crystal and in solution. *Helv. Chim. Acta* 68:682-704, 1985. (Cited 55 times.)
3. **Kessler H, Haupt A & Will M.** Design of conformationally restricted cyclopeptides for the inhibition of cholate uptake of hepatocytes. (Perun T & Probst K, eds.) *Computer aided drug design.* New York: Marcel Dekker, 1989. 461 p.
4. **Kessler H, Gehrke M & Griesinger C.** Two-dimensional NMR spectroscopy: background and overview of the experiments. *Angew. Chem. Int. Ed.* 27:490-536, 1988. (Cited 65 times.)
5. **Schmieder P, Kessler H & Oschkinat H.** Fast heteronuclear 3D-NMR spectroscopy. *Angew. Chem. Int. Ed.* 29:546-8, 1990.

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